Earlier defibrotide initiation post-diagnosis of veno-occlusive disease/sinusoidal obstruction syndrome improves Day +100 survival following haematopoietic stem cell transplantation

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Summary

Hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a progressive, potentially fatal complication of conditioning for haematopoietic stem cell transplant (HSCT). The VOD/SOS pathophysiological cascade involves endothelial-cell activation and damage, and a prothrombotic-hypofibrinolytic state. Severe VOD/SOS (typically characterized by multi-organ dysfunction) may be associated with >80% mortality. Defibrotide is approved for treating severe hepatic VOD/SOS post-HSCT in the European Union, and for hepatic VOD/SOS with renal or pulmonary dysfunction post-HSCT in the United States. Previously, defibrotide (25 mg/kg/day in 4 divided doses for a recommended ≥21 days) was available through an expanded-access treatment protocol for patients with VOD/SOS. Data from this study were examined *post-hoc* to determine if the timing of defibrotide initiation post-VOD/SOS diagnosis affected Day +100 survival post-HSCT. Among 573 patients, defibrotide was started on the day of VOD/SOS diagnosis in approximately 30%, and within 7 days in >90%. The relationship between Day +100 survival and treatment initiation before/after specific days post-diagnosis showed superior survival when treatment was initiated closer to VOD/SOS diagnosis with a statistically significant trend over time for better outcomes with earlier treatment initiation ($P < 0.001$). These results suggest that initiation of defibrotide should not be delayed after diagnosis of VOD/SOS.

Keywords

Introduction

Hepatic veno-occlusive disease, also called sinusoidal obstruction syndrome (VOD/SOS), is an unpredictable, potentially life-threatening complication of haematopoietic stem cell transplant (HSCT) conditioning (Bearman, 1995; Mohty *et al*, 2015) that also may occur as a result of primary chemotherapy, immuno-toxin conjugate therapy, or radiation (Fan & Crawford, 2014; Helmy, 2006). The hallmark clinical signs and symptoms of VOD/SOS include weight gain, hyperbilirubinaemia, ascites and painful hepatomegaly (Dignan *et al*, 2013; Mohty *et al*, 2016). The reported incidence of VOD/SOS has ranged widely (0–62%), varying by type of transplant, diagnostic criteria used and population risk factors (Mohty *et al*, 2016; Coppell *et al*, 2010). However, even with reduced-intensity conditioning, a VOD/SOS incidence of approximately 9% in allogeneic transplant patients has been reported (Tsirigotis *et al*, 2014) and of 11% in patients with acute lymphoblastic leukaemia receiving inotuzumab ozogamicin without HSCT (Kantarjian *et al*, 2016). Severe VOD/SOS, which is typically characterized by the presence of renal and/or pulmonary dysfunction (multi-organ dysfunction [MOD]) (Dignan *et al*, 2013; Mohty *et al*, 2016), may develop in approximately 20–40% of patients with VOD/SOS who received allogeneic HSCT (Carreras *et al*, 2011), and is associated with a mortality rate of >80% (Coppell *et al*, 2010).

VOD/SOS develops via a progressive cascade of pathophysiological events that generate a prothrombotic-hypofibrinolytic state (Fan & Crawford, 2014; Kumar *et al*, 2003; Carreras & Diaz-Ricart, 2011; Palomo *et al*, 2010; Richardson *et al*, 2013). The initial toxic injury occurs to sinusoidal endothelial cells and hepatocytes in zone 3 of the liver acinus, causing

endothelial cell activation, which in turn both triggers and supports an inflammatory response (Bearman, 1995; Carreras & Diaz-Ricart, 2011). The injured sinusoidal endothelial cells round up and slough off the endothelial wall, compromising its integrity, and permitting extravasation of blood into the space of Disse, which leads to thrombosis and extraluminal compression of the sinusoidal vessels (Fan & Crawford, 2014; Carreras & Diaz-Ricart, 2011). Endothelial cell injury also leads to upregulation of prothrombotic pathways, resulting in platelet activation, aggregation and sinusoidal thrombosis (Fan & Crawford, 2014; DeLeve *et al*, 2002). These developments cause further deterioration of the vasculature (Carreras & Diaz-Ricart, 2011). Profound endothelial dysfunction may result, accompanied by cytokine release and inflammation, with subsequent post-sinusoidal portal hypertension and the potential for hepatorenal syndrome, which manifests as MOD, and may progress rapidly to advanced MOD and death (Bearman, 1995; DeLeve *et al*, 2002; Ho *et al*, 2007).

Diagnosis of VOD/SOS has traditionally been based on Baltimore (Jones *et al*, 1987) or modified Seattle criteria (McDonald *et al*, 1993; Corbacioglu *et al*, 2012). However, these criteria were developed in an era when the risk/benefit ratio of available treatments was unfavourable (Mohty *et al*, 2016). More recently, an expert committee of the European Society for Blood and Marrow Transplantation (EBMT) challenged specific aspects of these criteria on the grounds that they may exclude or delay identification of some patients with VOD/SOS (Mohty *et al*, 2015). The EBMT emphasis on early intervention in management of VOD/SOS was in part prompted by the recent availability of effective therapy for this syndrome (Mohty *et al*, 2016). Defibrotide is now approved in the United States for treatment of adult and paediatric patients with hepatic VOD/SOS with renal or pulmonary dysfunction post-HSCT (http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208114lbl.pdf, accessed 30 August 2016), and is also approved in the European Union for treatment of severe hepatic VOD/SOS post-HSCT (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002393/WC500153150.pdf, accessed 30 August 2016). In a phase 3, historically controlled, clinical trial ($N = 134$), defibrotide treatment in patients with established hepatic VOD/SOS and MOD was associated with a statistically significant 23% improvement in survival rates ($P = 0 \cdot 0109$, propensity-adjusted analysis) at Day +100 post-HSCT (Richardson *et al*, 2016). *In vitro* data suggest that defibrotide may decrease activation of endothelial cells, thereby stabilizing and protecting them, and promoting the restoration of thrombofibrinolytic balance, as well as having anti-inflammatory effects (Palomo *et al*, 2010; Richardson *et al*, 2013; Pescador *et al*, 2013).

Monitoring for VOD/SOS, early diagnosis and timely treatment are crucial for post-HSCT patients. Determining the optimal time to initiate defibrotide treatment and its potential impact on outcomes is of high clinical interest. A *post-hoc* analysis from a defibrotide expanded-access treatment (T-IND) protocol for hepatic VOD/SOS (NCT00628498) was performed to investigate this issue.

Methods

The T-IND study was the largest prospective evaluation of defibrotide (25 mg/kg/day in 4 divided doses for at least 21 days) for the treatment of confirmed VOD/SOS, with and without MOD, in patients post-HSCT or post-chemotherapy. This exploratory analysis included all patients enrolled from 14 December 2007 to 31 December 2013, and data were reported to 5 December 2014. Study methods were previously reported (Richardson *et al*, 2015a); briefly, patients were initially eligible if they had VOD/SOS by Baltimore criteria (21 days post-HSCT, bilirubin 34.2 μmol/l and two or more of the following: hepatomegaly, ascites, weight gain 5%) (Jones *et al*, 1987) with associated MOD following HSCT. Following amendments to the protocol, patients were eligible if they were diagnosed with VOD/SOS by biopsy (Amendment 1 in December 2007), with or without MOD or following HSCT or chemotherapy (Amendment 2 in August 2009), or met Baltimore or modified Seattle criteria (20 days post-HSCT, with two or more of the following: bilirubin 34.2 μmol/l, hepatomegaly, or right upper quadrant pain, using a weight gain criterion of 5%) (McDonald *et al*, 1993; Corbacioglu *et al*, 2012) (Amendment 5 in August 2012). Key exclusion criteria were clinically significant bleeding or the need for 2 vasopressors. Concomitant medications that could increase the risk of bleeding must have been discontinued within 12 h of defibrotide administration.

The T-IND protocol recommended treatment with defibrotide at a dose of 25 mg/kg/day in 2-h intravenous infusions every 6 h for at least 21 days. The protocol-specified recommendation for treatment initiation stated: "The patient should receive their first dose of defibrotide as soon as the patient meets eligibility requirements." Patients were followed for 100 days after HSCT or the start of non-transplant–associated chemo/radiotherapy, and the primary efficacy evaluation was survival rate at Day +100.

This *post-hoc* analysis examined Day +100 survival in HSCT patients based on time from VOD/SOS diagnosis to initiation of defibrotide. Two analyses of Day +100 survival rate were performed:

■Analysis by treatment initiation for the entire HSCT population, comparing Day +100 survival rates before and after initiation on each of the following days: 1, 2, 3, 4, 7, and 14, from diagnosis date (using Fisher's exact test, calculated for patients with known survival status)

■Analysis of trend in Day +100 survival rates for only those patients with treatment initiated on a particular day or period: 0, 1, 2, 3, 4, 5, 6, 7, 8–14, and 15 days from diagnosis date using the Cochran-Armitage test for trend

P-values < 0.05 were considered statistically significant.

Results

The date of initial treatment with defibrotide was available for 573 HSCT patients in the T-IND programme, including 351 (61·3%) with MOD. Baseline characteristics of the total HSCT group and subgroup with MOD were similar. The mean age was 20·6 years overall, and 21·1 and 19·7 in the groups with and without MOD, respectively (Table I). In the

paediatric group of 319 patients (55·7%) aged younger than 16 years, 92 (28·8%) were younger than 1 year; 159 (49·8%) were aged 2–11 years; and 68 (21·3%) were 12–16 years.

Approximately half of the 573 HSCT patients had a primary diagnosis of acute leukaemia (165 [28·9%] with acute myeloid leukaemia and 118 [20·7%] with acute lymphocytic leukaemia). Other primary diseases in 5% of patients were neuroblastoma in 43 patients (7·5%), myelodysplastic syndrome in 33 patients (5·8%), and non-Hodgkin lymphoma in 29 patients (5·1%).

The vast majority of these patients received allogeneic HSCT: 503/573 (87·8%). Of the remaining 70 patients, 68 (11·9%) received autologous HSCT, and the transplant type was unknown for 2 patients (0·3%).

Overall, 31·9% of patients received defibrotide on the day of diagnosis, and it was started in 93·0% of patients by day 7 post-diagnosis. Between those dates, defibrotide treatment was started by day 1 in 59·7% of patients, by day 2 in 73·6%, by day 3 in 81·8%, by day 4 in 87·3%, by day 5 in 90·1% and by day 6 in 91·1%.

In the post-HSCT population-wide analysis of treatment initiation before or after days 0, 1, 2, 3, 4, 5, 6, 7 and 14 following VOD/SOS or VOD/SOS with MOD diagnosis, earlier initiation of defibrotide was associated with higher survival rates (Table II). Differences in survival rates before and after each of the temporal cut-off points ranged from 8·8% for patients with defibrotide initiated 1 or >1 day after diagnosis to 22·1% for patients with defibrotide initiated 2 or >2 days after diagnosis – this was statistically significant at all cut-off points assessed except day 14, although only 2·8% of patients began treatment post-day 14. For the VOD/SOS with MOD subgroup, Day +100 survival differences before and after each cut-off point ranged from 12·8% for patients with defibrotide initiated 1 or >1 day after diagnosis to 25·6% for patients with defibrotide initiated 2 or >2 days after diagnosis, and were statistically significant at all cut-off points except day 14; only 3·1% of patients with MOD began treatment after day 14.

In the post-HSCT with VOD/SOS cohort, the analysis of the relationship between Day +100 survival and treatment initiation day based on specific days or periods (0, 1, 2, 3, 4, 5, 6, 7, 8–14 and 15 days) found that there was a statistically significant trend over time (Cochran-Armitage test) for improved Day +100 survival with earlier treatment initiation ($P < 0.001$) (Fig 1). Similar improvement with earlier treatment initiation was shown for the subgroup of patients with MOD ($P < 0.001$).

The overall Day +100 survival rate of 45% in post-HSCT patients with VOD/SOS and MOD ($n = 387$) in this expanded-access programme (Richardson *et al*, 2015b) compares favourably with survival rates in the literature for patients with severe VOD/SOS receiving only supportive care (usually <25% survival) (Coppell *et al*, 2010). Safety data from the expanded-access programme further show that defibrotide was generally well tolerated, and drug-related toxicities were consistent with prior studies ((http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208114lbl.pdf, accessed 30 August 2016; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002393/WC500153150.pdf, accessed 30 August 2016)).

Discussion

The results of this exploratory *post-hoc* analysis show that in the overall post-HSCT with VOD/SOS population and in the subgroup with MOD, earlier initiation of defibrotide treatment from time of diagnosis of VOD/SOS was associated with significantly greater Day +100 survival compared to later treatment initiation. Further, in this study, there was no clinically apparent plateau where greater delay would not reduce survival.

There appear to be benefits to therapeutic intervention for VOD/SOS as early as possible following diagnosis, when the disease state may be more favourable for response (Mohty *et al*, 2016); prompt use of defibrotide in particular also has been emphasized in prior publications (Dignan *et al*, 2013; Mohty *et al*, 2016). In the present study, nearly a third of patients were treated on the day of diagnosis and almost three-quarters received treatment within the first 2 days post-diagnosis. In addition, mortality rates among these patients were below 50%, an outcome that also supports the T-IND protocol recommendation, that treatment begin as soon as the patient met eligibility requirements.

In the T-IND programme, patients were to receive defibrotide as soon as eligibility requirements were met; however, 28% received defibrotide on day 1 post-diagnosis, 14% on day 2, 8% on day 3, 5% on day 4, 3% on day 5, 1% on day 6, 2% on day 7 and 7% of patients received defibrotide even later. Factors contributing to any treatment delay were not captured consistently, but may have included ineligibility to receive defibrotide immediately as a result of active bleeding, haemodynamic instability, receipt of multiple vasopressors (a protocol-specified contraindication to defibrotide treatment based on theoretical safety concerns for infusional-related hypotension), delayed availability of defibrotide at the medical centre, delays while awaiting test results to confirm VOD/SOS, and/or diagnostic uncertainty.

The benefit of treatment with defibrotide for VOD/SOS may be associated with its ability to stabilize and protect endothelial cells via multiple pathways, as demonstrated *in vitro*, and thus counteract the pathogenic cascade of thrombotic/hypofibrinolytic processes of VOD/SOS within the endothelium that drive the development of hepatorenal syndrome and MOD (Carreras & Diaz-Ricart, 2011; Palomo *et al*, 2010; Richardson *et al*, 2013; Palomo *et al*, 2016). Preclinical data suggest that defibrotide's actions include increasing tissue plasminogen activator and thrombomodulin expression, promoting plasmin activity and angiogenesis, while inhibiting von Willebrand factor and plasminogen activator inhibitor-1 expression and fibrin deposition, and reducing inflammatory and oxidative factors and processes (Pescador *et al*, 2013; Palomo *et al*, 2016; Echart *et al*, 2009; Benimetskaya *et al*, 2008). *In vitro* data have shown that defibrotide exerts these actions through binding and interaction with endothelial cell membranes, and internalization by endothelial cells (Palomo *et al*, 2016). Because toxic injury to sinusoids is believed to be the initial pathogenic mechanism of VOD/SOS, defibrotide's actions in protecting and stabilizing endothelial cells from damage may provide a rationale for using it as early as possible post-diagnosis. Similarly, delayed diagnosis due to difficulty in definitively establishing VOD/SOS, potentially due to the highly dynamic nature of its signs and symptoms (Mohty *et al*, 2016), may also result in treatment being initiated later in disease progression. Conversely, even in

cases where treatment delay is unavoidable, the lack of a clear clinical cut-off for benefit in this analysis suggests that there is no point beyond which defibrotide initiation would not be warranted.

Few other analyses of the impact of timing of initiation of defibrotide on outcomes of VOD/SOS have been published. One retrospective study reported that early treatment with defibrotide post-diagnosis in patients with VOD/SOS and MOD was associated with a better outcome (Corbacioglu *et al*, 2004). For the 34 (76%) patients with a complete response (CR; resolution of VOD/SOS- and MOD-related symptoms and bilirubin <34.2 μmol/l), the average delay from VOD/SOS diagnosis to start of defibrotide therapy was 1 day vs. 5·5 days in patients without CR ($n = 11$; $P < 0·01$); this difference also was observed in the subgroup with VOD/SOS and MOD (1·3 days for those with CR vs. 5·5 days for those without CR; $P < 0·01$). A maximum delay of 1 day to initiate treatment vs. more than 1-day delay was the only significant predictor of CR identified (Corbacioglu *et al*, 2004).

Conclusions

This *post-hoc* analysis found that earlier initiation of defibrotide post-diagnosis was associated with increased Day +100 survival in the overall post-HSCT with VOD/SOS population and in the subgroup with MOD. No specific day post-diagnosis appeared to provide a viable cut-off resulting in better outcome, but earlier treatment initiation consistently provided more favourable clinical benefit in this population.

Acknowledgments

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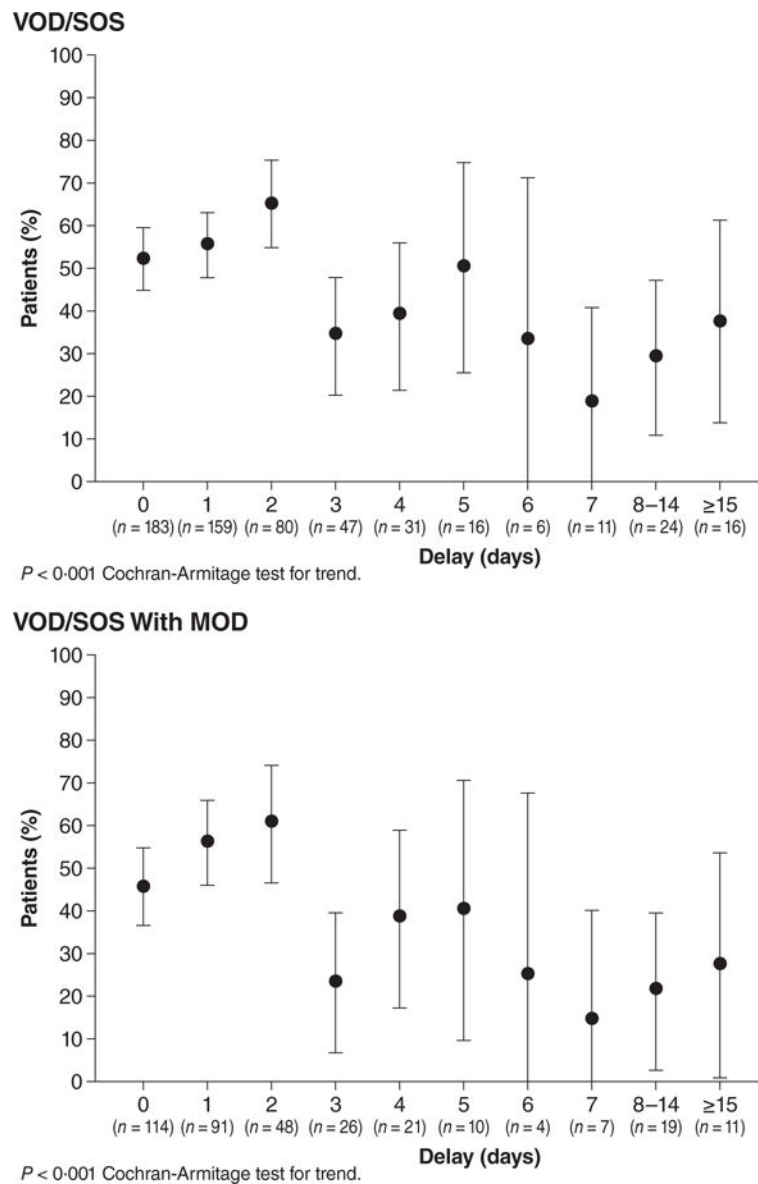
VOD/SOS

P < 0·001 Cochran-Armitage test for trend.

VOD/SOS With MOD

P < 0·001 Cochran-Armitage test for trend.

Fig 1. Day +100 survival by day of dosing (*P*<0.001 by Cochran-Armitage test for trend)[a]
[a]Bars around point estimates denote 95% confidence intervals.

Note: Among all HSCT VOD/SOS patients, 13 with a recorded negative dosing delay were adjusted to have 0 days dosing delay; 1 patient with −293 days dosing delay was excluded from this analysis. In the subgroup with MOD, 12 patients with a recorded negative dosing delay were adjusted to have 0 days dosing delay.

HSCT, haematopoietic stem cell transplantation; MOD, multi-organ dysfunction; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome.

Table I

Baseline demographic and clinical characteristics of HSCT patients who received defibrotide.

Variable	All HSCT Patients (*N* = 573)	HSCT Patients Without MOD (*n* = 222)	HSCT Patients With MOD (*n* = 351)
Gender, n (%)			
Male	324 (56·5)	140 (63·1)	184 (52·4)
Female	249 (43·5)	82 (36·9)	167 (47·6)
Race, n (%)			
White	374 (65·3)	137 (61·7)	237 (67·5)
Non-white	199 (34·7)	85 (38·3)	114 (32·5)
Age at HSCT, years			
Mean (SD)	20·6 (19·9)	19·7 (20·3)	21·1 (19·6)
Median (range)	14·0 (0·1–69·0)	13·5 (0·1–69·0)	15 (0·1–69·0)
Age category at HSCT, n (%)			
<16 years	319 (55·7)	130 (58·6)	189 (53·8)
16 years	254 (44·3)	92 (41·4)	162 (46·2)
Weight (kg)			
Mean (SD)	47·8 (31·3)	45·2 (30·8)	49·4 (31·5)
Median (range)	50·4 (3·0–134·5)	47·7 (3·0–118·6)	52·8 (3·2–134·5)
GVHD prophylaxis, n (%)			
None	81 (14·1)	37 (16·7)	44 (12·5)
Ciclosporin	189 (33·0)	71 (32·0)	118 (33·6)
Methotrexate	188 (32·8)	77 (34·7)	111 (31·6)
Sirolimus	64 (11·2)	17 (7·7)	47 (13·4)
Tacrolimus	264 (46·1)	98 (44·1)	166 (47·3)
Other	184 (32·1)	72 (32·4)	112 (31·9)
Type of HSCT, n (%)			
Allograft	503 (87·8)	186 (83·8)	317 (90·3)
Autograft	68 (11·9)	34 (15·3)	34 (9·7)
Unknown	2 (0·3)	2 (0·9)	0 (0·0)

GVHD, graft-versus-host disease; HSCT, haematopoietic stem cell transplantation; MOD, multi-organ dysfunction; SD, standard deviation.

Table II

Day +100 survival by defibrotide initiation day.

Initiation Period	HSCT VOD/SOS (N = 573)			HSCT VOD/SOS With MOD (n = 351)		
	Alive n (%)	Dead n (%)	Unknown n (%)	Alive n (%)	Dead n (%)	Unknown n (%)
1 day[a]	183 (53·5)	142 (41·5)	17 (5·0)	103 (50·2)	93 (45·4)	9 (4·4)
>1 day	105 (45·5)	116 (50·2)	10 (4·3)	56 (38·4)	85 (58·2)	5 (3·4)
Difference (95% CI)[b]	8·8% (0·2–17·3%)			12·8% (2·0–23·4%)		
P-value[c]	0·045			0·021		
2 days	235 (55·7)	166 (39·3)	21 (5·0)	132 (52·2)	111 (43·9)	10 (4·0)
>2 days	53 (35·1)	92 (60·9)	6 (4·0)	27 (27·6)	67 (68·4)	4 (4·1)
Difference (95% CI)[b]	22·1% (12·6–31·2%)			25·6% (13·8–36·9%)		
P-value[c]	<0·001			<0·001		
3 days	251 (53·5)	193 (41·2)	25 (5·3)	138 (49·5)	129 (46·2)	12 (4·3)
>3 days	37 (35·6)	65 (62·5)	2 (1·9)	21 (29·2)	49 (68·1)	2 (2·8)
Difference (95% CI)[b]	20·3% (9·6–30·8%)			21·7% (8·6–34·5%)		
P-value[c]	<0·001			0·001		
4 days	263 (52·6)	212 (42·4)	25 (5·0)	146 (48·7)	142 (47·3)	12 (4·0)
>4 days	25 (34·2)	46 (63·0)	2 (2·7)	13 (25·5)	36 (70·6)	2 (3·9)
Difference (95% CI)[b]	20·2% (7·7–32·4%)			24·2% (9·1–38·9%)		
P-value[c]	0·002			0·002		
7 days	275 (51·6)	232 (43·5)	26 (4·9)	152 (47·4)	156 (48·6)	13 (4·0)
>7 days	13 (32·5)	26 (65·0)	1 (2·5)	7 (23·3)	22 (73·3)	1 (3·3)
Difference (95% CI)[b]	20·9% (4·5–37·1%)			25·2% (6·1–43·8%)		
P-value[c]	0·013			0·011		
14 days	282 (50·6)	249 (44·7)	26 (4·7)	156 (45·9)	171 (50·3)	13 (3·8)
>14 days	6 (37·5)	9 (56·3)	1 (6·3)	3 (27·3)	7 (63·6)	1 (9·1)

	HSCT VOD/SOS (N = 573)			HSCT VOD/SOS With MOD (n = 351)		
Initiation Period	Alive n (%)	Dead n (%)	Unknown n (%)	Alive n (%)	Dead n (%)	Unknown n (%)
Difference (95% CI)[b]		13·1% (−12·9 to 39·5%)			17·7% (−14·6 to 51·5%)	
P-value[c]		0·433			0·344	

[a] Among all HSCT VOD/SOS patients, 13 with a recorded negative dosing delay were adjusted to have 0 days dosing delay; 1 patient with −293 days dosing delay was excluded from this analysis. In the MOD subgroup, 12 patients with a recorded negative dosing delay were adjusted to have 0 days dosing delay.

[b] Alive and dead. 95% CI calculated using exact method.

[c] Fisher's exact test, alive and dead.

CI, confidence interval; HSCT, haematopoietic stem cell transplantation; MOD, multi-organ dysfunction; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome.